Sex difference of regional activation in the rat brain using manganese-enhanced magnetic resonance imaging

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INTRODUCTION: Since the morphological difference between sexes in the medial preoptic area was reported [1], sex differences of the rodent brain have been observed in numerous regions. Manganese-enhance magnetic resonance imaging (MEMRI) is becoming a useful tool for visualizing brain anatomical structure and regional activity *in vivo* [2]. Manganese ion can pass through blood-brain barrier, enter the firing neurons via voltage-gated calcium channel and be transported to the next neuron [3]. Manganese ion is itself paramagnetic. Therefore, MEMRI can be utilized to demarcate the regions and tracts activated by the stimuli outside the magnet [4]. These regions of enhanced signal intensities in the image by the MEMRI had the spatial overlaps with those of the blood oxygenation level-dependent signal intensities by the fMRI [5]. Using MEMRI, we investigated sex differences in the brain activation for one day.

MATERIALS AND METHODS: Twenty Sprague-Dawley rats (male = 10, female = 10) at 9 weeks of age and 210 - 350 g of body weight were used in this study. The $MnCl_2$ solution was prepared at a concentration of 50 mM in saline, and rats were injected intraperitoneally with 60 mg/kg body weight of $MnCl_2$. All images were acquired using a 4.7 T / 40 cm horizontal magnet equipped with a Bruker BioSpec console and an actively decoupled quadrature rat head surface coil for receive-only. The surface coil was located using the position of rat's eye to minimize inter-subject positional difference. Three-dimensional data set of T1-weighted images was acquired using a modified driven equilibrium Fourier transform (MDEFT) pulse sequence with TE = 3.8 ms, TR = 15 ms, Matrix = 256 x 234 x 86, FOV = 3.84 x 3.51 x 2.58 cm^3, voxel resolution = 150 x 150 x 300 μm^3, number of sequences = 4, number of averages = 2. Brain images were obtained 24 - 30 hours later after the infusion of $MnCl_2$, and in the mean time, no specific stimulus or task was given to animals. To compare the regional brain activity between sexes, alignments of all brains to stereotaxic space were needed. We used the co-registration protocol similar to the 'optimized Voxel-Based Morphometry' style using FSL [6].

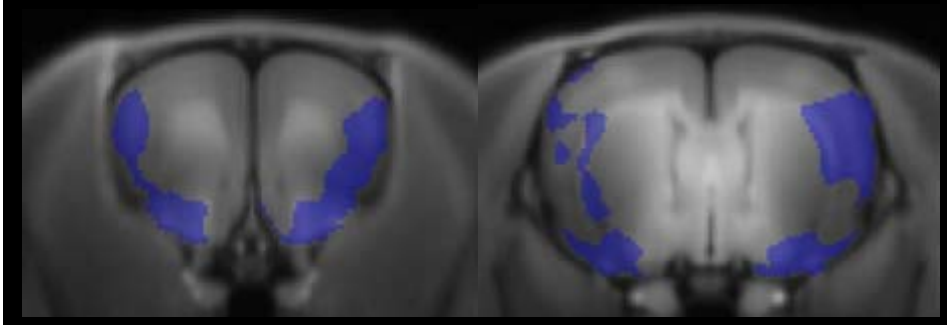

Fig. 1. Brain area with higher signal intensity in male rat.

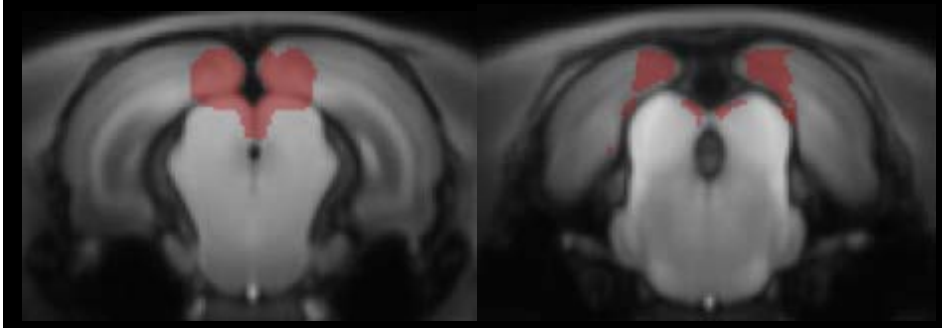

Fig 2. Brain area with higher signal intensity in female rat.

RESULTS : In the brains of male rats compared to those of female rats, regions with significantly enhanced signal intensities were found mainly on the olfactory pathway, insula, lateral orbital cortex, ventral pallidum, primary and secondary somatosensory cortex, and external capsule adjacent to the activated somatosensory cortex (Fig 1. two-sample t test, $p < 0.05$, FDR corrected for multiple comparisons). In the brains of female rats compared to those of male rats, regions with significantly enhanced signal intensities were found mainly on restrosplenial cortex, primary and secondary visual cortex, superior colliculus, inferior colliculus, periacueductal gray matter (Fig. 2, two-sample t test, $p < 0.05$, FDR corrected).

DISCUSSION: Until now, there have been numerous neuroimaging studies on sexual dimorphism of rodent brain structure, while those of rodent brain activity using functional imaging technique had not been examined yet.

In the current study, we used MEMRI for investigating sex difference in regional activity of rat brain without any specific task in home cage. We found that male rats had enhanced brain activation in the olfactory system including lateral olfactory tract, piriform, and amygdala. On the while, female rats had enhanced brain activation in the visual system including primary and secondary visual cortex, and superior colliculus.

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